Azixa, a Microtubule Destabilizing Agent, in Solid Tumors: Results of a Phase 1 Trial
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**Background**

- **MPC-6827 (Azixa)**: A 4-arylaminoquinazoline is a small molecule microtubule destabilizing agent that causes mitotic arrest and cell death
- In vitro, MPC-6827 displayed proapoptotic activity, with potency at low nanomolar concentrations in a broad spectrum of cancer cells
- In mice, MPC-6827 significantly inhibited the growth of a variety of subcutaneously implanted tumor lines.
- MPC-6827 has also been shown to be a vascular-disrupting agent (VDA) in a human ovarian OVCAR-3 carcinoma xenograft
- VDAs have been established to reduce interstitial pressure in the tumor microenvironment, which may increase local exposure to cytotoxic chemotherapy

**Patients and Methods**

- Patients with advanced or metastatic cancer were treated with once-weekly intravenous (IV) infusion for 3 weeks every 28 days
- Dose escalation began with 0.3, 0.6, 1, and 1.5 mg/m²
- Subsequent increments of 0.6 mg/m² were given until the MTD was determined
- A conventional "3 + 3" design was used
- Responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST)

**Definition of DLT**

- ≥ Grade (G) 3 nonhematologic toxicity (excluding nausea/vomiting or alopecia)
- ≥ Grade 3 nausea/vomiting uncontrolled by aggressive antiemetic support
- G4 neutropenia lasting > 5 days
- Any febrile G3-4 gastritis
- G4 thrombocytopenia or ≥ Grade 3 toxicology without resolution within 72 hrs

**Pharmacokinetics**

- Plasma concentrations of MPC-6827 and its O-demethyl metabolite, MPI-0440627 were determined after the first and third IV infusions during cycle 1 (i.e. on study days 1 and 15).
- Blood samples were collected before MPC-6827 administration, at the end of drug infusion, and at 1, 2, 4, 6, 12, and 24 hours post-infusion

**Antitumor activity**

- All subjects underwent a CT scan or MRI at screening, at Day 28 ± 7 days, and every 28 ± 7 days thereafter until the end of the study, and at the final visit

**Parameters for MTD**

- **Redistributions**
  - $t_{1/2A}$ (parent): 8.16
  - $t_{1/2B}$ (metabolite): 12.90
  - $C_{max, AUC}$, Day 1: 22.82
  - Day 1: MPC-6827 (parent): 15.10
  - Day 15: MPC-6827: 19.11
  - Day 15: MPI-0440627 (metabolite): 3.58
- **Mean Parameters for MTD of 3.3 mg/m², Cmax, and AUC (0-24 hr)**
  - Parent mean concentrations are shown with circles, while metabolite concentrations are shown with triangles.
  - The best fit line for parent is a solid line, while the best fit for metabolite is a dashed line.

**Stable Disease (N=5)**

- **6508**
  - 40 years
  - Breast: 1
  - Male: 1
  - Female: 3
  - No. of prior therapies: 1
  - Karnofsky PS: 90
  - Viable Rim: 1080
  - MST-997 + zoledronic acid, docetaxel + zoledronic acid + cinacalcet hydrochloride

**Adverse Events (I)**

- **Day 0**
  - Hypoesthesia: 2
  - Fatigue: 2
  - Hypotension: 1
  - Anorexia: 1
  - Insomnia: 1
  - Pruritus: 1
  - Myalgia: 1
  - Pain in extremity: 1
  - Pain: 1
  - Anemia: 1

- **Day 1**
  - Hypoesthesia: 2
  - Fatigue: 1
  - Hypotension: 1
  - Anorexia: 1
  - Insomnia: 1
  - Pruritus: 1
  - Myalgia: 1
  - Pain in extremity: 1
  - Pain: 1
  - Anemia: 1

- **Day 7**
  - Hypoesthesia: 1
  - Fatigue: 2
  - Hypotension: 1
  - Anorexia: 1
  - Insomnia: 1

**Conclusions**

- MPC-6827 was well tolerated up to and including the MTD of 3.3 mg/m² IV once weekly for 3 weeks
- Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) maps of $K_{trans}$ in a patient with a large primary non-small cell lung cancer of the right upper lobe